



Nursing Interventions Targeting Fatigue in Inflammatory Bowel Disease: A Systematic Review

Matteo Martinato ^{1,*}, Elena Boffo ¹, Greta Lorenzon ², Eleonora Monaco ¹, Clara Iervolino ³, Rosanna Irene Comoretto ³, Edoardo Vincenzo Savarino ² and Dario Gregori ¹

- ¹ Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, 35131 Padova, Italy; elena.boffo@aulss7.veneto.it (E.B.); fedele9297@gmail.com (E.M.); dario.gregori@ubep.unipd.it (D.G.)
- ² Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova, 35128 Padova, Italy; gretalorenzon90@gmail.com (G.L.); edoardo.savarino@unipd.it (E.V.S.)
- ³ Department of Sciences of Public Health and Pediatrics, University of Torino, 10100 Turin, Italy; clara.iervolino@edu.unito.it (C.I.); rosannairene.comoretto@unito.it (R.I.C.)
- * Correspondence: matteo.martinato@ubep.unipd.it; Tel.: +39-347-2306806

Abstract: A prevalent symptom among Inflammatory Bowel Disease (IBD) patients is fatigue, characterized by a persistent sense of energy depletion that affects all aspects of daily life. This review aims to evaluate nursing interventions reported in the literature to alleviate fatigue in IBD patients. A comprehensive search was conducted across four electronic databases—PubMed, CINAHL, Cochrane, and Scopus—and four scientific journals: "Gastroenterology", "Inflammatory Bowel Disease", "Journal of Crohn's and Colitis", and "United European Gastroenterology Journal". Inclusion criteria were clinical trials involving adult IBD patients in remission or mild disease activity. Out of 234 studies, 2 were selected for review. These studies assess the effectiveness of Solution-Focused Therapy (SFT) that emphasizes solving problems and developing strategies for improvement, and Problem-Solving Therapy (PST) that focuses on identifying problems and coping strategies. SFT showed a positive impact on fatigue with a significant improvement in the Checklist Individual Strength after three months: 45.5% in the control group, 85.7% in the SFT group, and 60% in the PST group, but its impact declined over time. Additionally, SFT demonstrated potential for reducing healthcare costs compared to standard of care and PST. Further research is needed to provide nurses interventions for managing fatigue in IBD patients. The review protocol has been registered at OSF.io.

Keywords: IBD; fatigue; nursing

1. Introduction

1.1. Rationale

Inflammatory Bowel Disease (IBD) refers to idiopathic conditions characterized by chronic, relapsing inflammation of the gastrointestinal tract, typically manifesting in genetically predisposed individuals exposed to environmental risk factors [1]. The two most common forms are ulcerative colitis (UC), which affects only the large intestine, and Crohn's disease (CD), which can impact the entire digestive tract from the mouth to the anus [2].

Clinically, both conditions present with similar symptoms, such as abdominal pain, diarrhea, asthenia, and persistent fever [3], alongside macro- and microscopic evidence necessary for diagnosis. CD often affects the terminal ileum and initial part of the large intestine, causing transmural lesions that give a "cobblestone" appearance endoscopically [4]. According to the Montreal criteria [5], it is classified according to age of onset, location, and behavior (non-stenosing and non-fistulizing, stenosing, fistulizing and with perianal involvement). Symptoms include abdominal pain, diarrhea, abscesses, fistulas, and possible occlusive states due to stenosis [6].



Citation: Martinato, M.; Boffo, E.; Lorenzon, G.; Monaco, E.; Iervolino, C.; Comoretto, R.I.; Savarino, E.V.; Gregori, D. Nursing Interventions Targeting Fatigue in Inflammatory Bowel Disease: A Systematic Review. *Gastrointest. Disord.* **2024**, *6*, 706–719. https://doi.org/10.3390/ gidisord6030047

Academic Editors: Angharad Hurley (Vernon-Roberts) and Andrew Day

Received: 30 April 2024 Revised: 22 July 2024 Accepted: 29 July 2024 Published: 5 August 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). UC always involves the rectum, extends proximally, and affects only the mucosal layer, leading to classifications such as Proctitis, Left Colitis, Extensive Colitis, and Pan-Colitis. It commonly presents with bloody diarrhea, anemia, pus or mucus in stool, and tenesmus. Unlike CD, UC does not cause fistulas or strictures [7].

Both diseases may have extra-intestinal manifestations (EIMs) related to inflammatory activity and malabsorption, affecting joints, skin, liver, bones, and eyes [8].

1.1.1. Etiopathogenesis and Incidence

In recent decades, IBD has been extensively studied, but its etiopathogenesis remains not fully understood. A genetic component is known, with specific gene mutations linked to a higher likelihood of developing the disease. Studies show a high, but not complete, concordance in twins [9]. Environmental risk factors, such as infections, stress, oral contraceptives, and diet, also play a role in the development of IBD in genetically predisposed individuals [10]. Although the literature shows no substantial differences in incidence related to sex, there appears to be a higher incidence of UC in men and CD in women [11].

Since the latter half of the 20th century, the incidence of IBD has significantly increased, particularly in industrialized countries like Europe and North America [11]. A 2013 study by the European Crohn's and Colitis Organisation reported that, in 2010, the incidence of CD was 6.5/100,000 people in Western Europe and 3.1/100,000 in Eastern Europe, while UC incidence was 10.8/100,000 in Western Europe and 4.1/100,000 in Eastern Europe [12]. This indicates notable differences between Eastern and Western Europe, and between Northern and Southern Europe, with higher incidences in Northern Europe.

The prevalence of IBD in Europe ranges from 1.5 to 213 cases per 100,000 people for CD, and from 2.4 to 294 cases per 100,000 for UC [13]. Overall, about 1.6 million people in Europe are affected by CD and 2.1 million by UC, totaling 3.7 million people with IBD [14].

Socio-cultural and dietary changes over the past sixty years may have exposed genetically predisposed individuals to risk factors, leading to what is described as "an abnormal immune response against an external agent, causing inflammatory damage to the intestinal epithelium" [15]. Factors that can alter the gut's microbial balance include reduced fiber intake, increased consumption of processed foods, different eating habits, stress, and a more hectic lifestyle [10].

1.1.2. Direct and Indirect Costs

The management of IBD, like all chronic diseases, involves considerable expenses, both direct and indirect. Direct expenses include hospitalizations, pharmaceutical prescriptions, medications, diagnostic procedures, internist, psychiatric, physiatrist examinations, and psychological consultations. Among the indirect expenses, absences from work and in the long run the development of disabilities are more important [16].

Various studies have attempted to investigate the costs of direct care of these pathologies: in Europe, the expenditure is around 4.6–5.5 million euros per year [8], and the average annual cost per patient is around €4099 for CD, €2221 for UC, and €1607 for indeterminate colitis. With the introduction of biologics, the annual expenditure of individual patients has increased, but on the other hand, the need for other drugs and hospitalizations has decreased [17].

A relationship between the patient's level of knowledge and the decrease in annual costs has been studied: the more the patient has received a good education about his disease, anatomy, signs and symptoms, medications, the more the cost of managing the pathology is reduced [18]. Working on education and correct information is essential for the therapeutic path of these patients [19].

1.1.3. IBD and Fatigue

A symptom that characterizes IBD patients is fatigue. In the literature, it is defined as an overwhelming and disabling sense of constant exhaustion that impairs the ability to carry out normal daily activities, including the ability to carry out one's work and to fulfil one's family and social role [20].

There has never been a significant difference in the level of fatigue between UC and CD [21]. It is important to consider gender and age when measuring the level of fatigue; in fact, women typically have higher scores than men, and a higher age is correlated with an increased risk of perceiving the symptom [22].

Initially, it was thought that the symptoms of fatigue characterized only the phases in which the disease is active, but it has been shown that this sense of fatigue and exhaustion persists even in periods of remission [23]. In fact, up to 86% of patients experience fatigue in the active phase, but 40–83% also experience it in the remission phase [20].

The symptom of fatigue becomes chronic when it lasts more than six months [24]. Alongside the persistence of the problem, the patient's worry and level of anxiety about the disease also increase. All this must be added to the reduction in the quality of life from a family, psychological, social, and work point of view that results from the lack of energy [23].

Fatigue is a multidimensional phenomenon that must therefore be evaluated from several points of view: intensity/severity, frequency, duration, stress, physical impact, psychological impact [2].

At the base of fatigue, there is certainly the inflammatory response of the body, with the presence of numerous pro-inflammatory cytokines in circulation, malabsorption and dehydration that follow the diarrheal state, anemia that derives from ulcerations of the intestinal mucosa, and polypharmacotherapy [25].

It is also important to consider the drug treatments that patients are undergoing. Since these are inflammatory diseases with an autoimmune basis, the therapies available to reduce the inflammatory and infectious state are anti-inflammatory, antibiotic and immunomodulatory [26]. The presence of fatigue can therefore be due both to the action of the disease and to the state of immunosuppression caused by the therapies.

1.1.4. Nursing: What Interventions Can the Nurse Offer?

IBD presents several medical complications: fecal incontinence, fistula formation, pain, extra-intestinal complications, development of cancer, and disability [25]. From these arises the need for nursing assistance, in the management of devices, medications, and in the instruction of the patient towards the acquisition of a new autonomy [27].

The nurse has the task of supporting the patient in the following ways:

- Reducing the stress caused by other interventions to a minimum, understanding the needs and preferences of the individual patient, communicating with the patient using the most effective strategy, offering empathic support, and encouraging the patient to develop self-care skills so that he or she can play an active role in the management of the disease [27];
- Informing patients about the dietary rules to be followed to facilitate the remission of the disease and its maintenance, ensuring the patient has the right nutritional intake in the active stages of the disease, where even simple food intake can be difficult [28], and trying to make it clear that each individual patient will be able to achieve his or her own balance and that there are no rules that are the same for everyone [29];
- Identifying the patient's needs in the management of emotional aspects related to sexuality and the complications that the disease entails, changes in body image and functionality, dependence on drugs and therapies, and difficulty in acceptance [30].

From a nursing point of view, fatigue is a primary symptom to work on, but research offers very little information about it [31]. Some authors correlate it with a deficiency in iron, hemoglobin, or vitamin D [32], while, according to others, the presence of fatigue is not attributable exclusively to these deficiencies but must be evaluated holistically, taking into account the psychological and social impairment that the disease brings; it is in fact known that the establishment of anxious attitudes, depression, worsening of the disease are directly linked to the level of fatigue of the person [21]. It is necessary to be aware of

how important it is to identify patient steps and coping mechanisms, to manage fatigue, and facilitate rehabilitation and recovery of a good quality of life.

1.1.5. Why This Review Is Needed

For nurses and all healthcare professionals who work alongside these patients, fatigue remains a problem that is still poorly understood, not fully understood, and difficult to work on in clinical practice [22].

Nurses themselves, but not only nurses, declare the need for more information on what interventions are of proved efficacy and effectiveness [1]. With reference to direct patient care and psychological, familial, and relational support, it would be useful to deepen the usefulness of some interventions: painkillers, nutritional education, direct or indirect support [30].

In addition, research on strategies to reduce fatigue in IBD patients is one of the five priority points of investigation outlined by European IBD nurses in the article: Identification of Research Priorities for Inflammatory Bowel Disease Nursing in Europe: a Nurses-European Crohn's and Colitis Organisation Delphi Survey [33].

1.2. Objective of the Review

The objective of this review is to describe the effectiveness of nursing interventions aimed at alleviating the sense of fatigue in IBD patients.

2. Methods

2.1. Criteria Used for the Selection of Studies to Be Included in the Review

2.1.1. Types of Studies

All controlled trials (randomized and non-randomized), single or double-blind, single, or multicenter, and case-control studies were considered.

2.1.2. Types of Participants

All studies performed in adults (age > 18 years) with a clinical diagnosis of Crohn's disease, ulcerative colitis, or any other form of IBD and with a disease in remission or mild activity were included in the review. Studies in children and adolescents (age < 18 years) and pregnant women were excluded.

2.1.3. Types of Interventions

All studies with nursing interventions to alleviate fatigue were included: to be included, a study had to be aimed at relieving fatigue, as a primary or secondary outcome.

The interventions had to be carried out by nursing staff or in collaboration with other professionals.

The interventions could be carried out in any form (face-to-face, by telephone, via the internet) and in any setting (at home, in private or public facilities, in peer groups). Any non-nursing intervention was excluded.

2.1.4. Types of Outcome Measurements

Primary Outcomes

The primary outcome assessed in this review is fatigue; any study investigating an intervention to counteract decreased energy, fatigue, limited ability to perform daily activities, and so on has been included.

All studies were evaluated:

- 1. Assessing fatigue through validate measurement scales, such as the Severity Scale fatigue [34], Chalder Fatigue Scale [35], Fatigue Impact Scale [36,37], and Piper Fatigue Scale [38];
- In which fatigue, the loss of energy/vigor, emerges from a single question or from measuring instruments specifically created to assess the presence or absence of these symptoms;

- 3. Which include multidimensional assessments that analyze the sense of fatigue from multiple aspects, such as intensity, frequency, and severity, or that evaluate mental, physical, social, and affective involvement;
- 4. Proposing solutions and methodologies to alleviate the sense of fatigue, which then provide strategies to patients (through psychological and physical techniques, through group interventions or personal investigations).

Secondary Outcomes

Studies assessing quality of life (patient-reported), disease activity, resource consumption, hospitalizations, length of hospitalizations, number of outpatient visits, direct care costs, and indirect costs (lost working days) were included.

2.2. Search Strategy

2.2.1. Electronic Search

The search was performed in PUBMED, CINAHL, SCOPUS, and COCHRANE.

The search strategy was different for each database, and the limits imposed were as follows: studies involving humans, studies involving people >18 years old, studies involving nursing interventions.

Any pharmacological, medical, or surgical intervention, or any exclusively involving other healthcare professionals (psychologists, dieticians, physiotherapists) delivering the intervention under study, was excluded.

PUBMED Search Strategies

"Fatigue" [Mesh] AND ("Inflammatory Bowel Diseases" [Mesh] OR "Colitis, Ulcerative" [Mesh] OR "Crohn Disease" [Mesh]) AND ("Nurses" [Mesh] OR "Nursing" [Mesh] OR "Nursing Care" [Mesh])

fatigue[Title/Abstract] AND (inflammatory bowel disease[Title/Abstract] OR inflammatory bowel diseases[Title/Abstract] OR crohn's disease[Title/Abstract] OR ulcerative colitis[Title/Abstract]) AND (nurse[Title/Abstract] OR nursing[Title/Abstract] OR nursing care[Title/Abstract])

fatigue AND (inflammatory bowel diseas* OR crohn's disease OR ulcerative colitis) AND nurs*

CINAHL Search Strategies

(MH "Fatigue") AND (MH "Inflammatory Bowel Diseases" OR MH "Ulcerative Colitis" OR MH "Crohn's Disease") AND (MH "Nurses" OR MH "Nursing" OR MH "Nursing Care")

TI fatigue AND (TI inflammatory bowel disease OR TI inflammatory bowel diseases OR TI crohn's disease OR TI ulcerative colitis) AND (TI nurse OR TI nursing OR TI nursing care)

AB fatigue AND (AB inflammatory bowel disease OR AB inflammatory bowel diseases OR AB crohn's disease OR AB ulcerative colitis) AND (AB nurse OR AB nursing OR AB nursing care)

fatigue AND (inflammatory bowel diseas* OR crohn's disease OR ulcerative colitis) AND nurs*

SCOPUS Search Strategies

TITLE-ABS-KEY(fatigue) AND (TITLE-ABS-KEY("inflammatory bowel disease") OR TITLE-ABS-KEY("ulcerative colitis") OR TITLE-ABS-KEY("crohn's disease")) AND (TITLE-ABS-KEY(nurse) OR TITLE-ABS-KEY(nursing) OR TITLE-ABS-KEY("nursing care"))

TITLE-ABS-KEY(fatigue) AND (TITLE-ABS-KEY("inflammatory bowel disease") OR TITLE-ABS-KEY("inflammatory bowel diseases") OR TITLE-ABS-KEY("crohn's disease") OR TITLE-ABS-KEY("ulcerative colitis")) AND (TITLE-ABS-KEY(nurse) OR TITLE-ABS-KEY(nursing) OR TITLE-ABS-KEY("nursing care")) TITLE-ABS-KEY(fatigue) AND (TITLE-ABS-KEY("inflammatory bowel disease*") OR TITLE-ABS-KEY("crohn's disease") OR TITLE-ABS-KEY("ulcerative colitis")) AND TITLE-ABS-KEY(nurs*)

COCHRANE Search Strategies

fatigue AND ("inflammatory bowel diseases" OR "colitis, ulcerative" OR "crohn disease") AND ("nurses" OR "nursing" OR "nursing care")

fatigue AND ("inflammatory bowel disease" OR "inflammatory bowel diseases" OR "crohn's disease" OR "ulcerative colitis") AND (nurse OR nursing OR "nursing care")

fatigue AND (inflammatory bowel diseas* OR crohn's disease OR ulcerative colitis) AND nurs*

2.2.2. Research by Means of Other Resources

The articles published in the journals "Gastroenterology", "Inflammatory bowel disease", "Journal of Crohn's and colitis", and "United European Gastroenterology Journal" were analyzed; in particular, the supplements dedicated to the congresses organized by the European Crohn's and Colitis Organisation on the occasion of the Digestive Disease Week, the United European Gastroenterology Week, and the congress Advances in Inflammatory Bowel Diseases.

The articles reported in the references of the articles identified in the previous steps were also considered.

2.3. Selection Process

The selection of the data was carried out in steps by two independent reviewers: the first selection was made assessing the title, then the abstracts were read for a further selection of suitable articles, and finally the full texts of the articles considered suitable in the previous step were read in order to be able to analyze the content of the articles and extract useful elements for review. Disagreement between the two reviewers was resolved by a third reviewer.

2.4. Data Collection Process

To facilitate the analysis of the selected documents and the consultation of the results, study data, study design, intervention setting, duration of the intervention, type of participants, inclusion and exclusion criteria, method of placement in groups, intervention, control modalities, primary results, secondary results, and bias were extracted.

2.5. Review Protocol Registration

The review protocol has been registered at OSF.io (https://doi.org/10.17605/OSF.IO/ TJ4B6 accessed on 15 April 2024).

3. Results

3.1. Study Selection

Out of 234 studies identified by the literature search, 2 were identified. Figure 1 describes the selection process. The characteristics of the selected studies and data extracted are described in Table 1.

Of the 41 papers analyzed in the full text, only 2 propose interventions that have as their primary outcome the fatigue in IBD patients [39,40]. Other studies identify it as a secondary outcome or indirect consequence [41] obtained through interventions on stress and on the management and organization of daily activities.

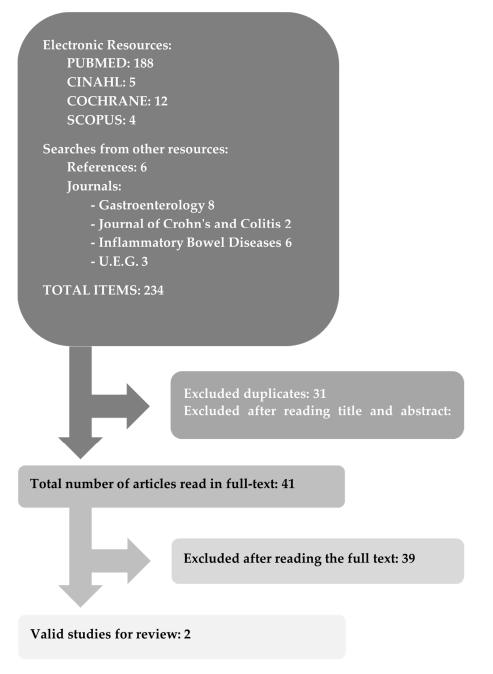


Figure 1. Prisma flowchart.

3.2. Study Characteristics

The two studies considered in this review are randomized controlled trials performed by the same researcher three years apart.

The first is a pilot study that aims to verify the effectiveness of two psychological interventions to reduce the sense of fatigue in CD patients: Solution-Focused-Therapy (SFT) and Problem-Solving-Therapy (PST). The therapies were performed in groups and were adapted according to the diagnosis of the patients [42].

	Article #1	Article #2
<u>Title</u>	Solution focused therapy: A promising new tool in the management of fatigue in Crohn's disease patients psychological interventions for the management of fatigue in Crohn's disease	Fatigue management in patients with IBD: a randomised controlled trial
Journal	Journal of Crohn's and Colitis	G.U.T
Date	2 June 2011	24 June 2013
Study design	randomized-controlled trial	randomized-controlled trial
Country	Netherlands	Netherlands
Allocation to groups	Random, 20 pcs in the control group, 10 in the Problem-Solving Therapy group, and 10 in the Solution Focused Therapy group	random, 49 pcs in the control group, and 49 in the Solution Focused Therapy group
<u>Selection</u> <u>criteria</u>	Inclusion criteria: patients with a degree of fatigue > 35% (according to CIS-20 questionnaire), patients with disease in remission (according to HBI questionnaire), patients with a value < 10 on the scales on quality of life and anxiety and depression (IBD-Questionnaire and HADS-Anxiety and Depression Scale).	Inclusion criteria: patients over 18 years of age, patients with a degree of fatigue > 35% (according to the CIS-20 questionnaire), patients with disease in remission (according to the HBI questionnaire), patients with a value < 10 on the scales on quality of life and anxiety and depression (IBD-Questionnaire and HADS-Anxiety and Depression Scale). Exclusion criteria: patients with active or acute
	Exclusion criteria: patients with active or acute illness (according to HBI questionnaire), pregnant patients, lactating patients, patients suffering from short bowel syndrome, cancer patients, and patients suffering from psychiatric disorders.	illness (according to HBI questionnaire), pregnant patients, lactating patients, patients with short bowel syndrome, cancer patients, patients with psychiatric disorders, patients with other bowel disorders, patients with kidney, infectious, hepatic, cardiological diseases, patients who have performed interventions in the last 12 months, patients who have a history of substance or alcohol abuse.
<u>N° enrolled</u>	40	98
Gender:	72% women, 28% men	63% women, 37% men
Disease	CD in remission	UC or CD indifferently, disease in remission, or mildly active
<u>Results:</u>	 CIS total score after 3 months: decrease in 45.5% of patients (control group), 85.7% (SFT group), 60% (PST group). No significant differences were observed between the groups. Costs: decrease in 45.5% of patients (control croup), 57.1% (SFT group), 20% (PST group). No significant differences were observed between the groups. Quality of life (IBDQ total score): the intervention groups showed more patients with improved scores than the control patients from baseline to follow-up (SFT 71.4%, PST 60%, control group 50%). No significant differences were observed between the groups. Anxiety and depression (HADS scale): all patients remained under the score of 10 points, meaning no clinically significant depression or anxiety occurred during the 6-month study period. 	CIS total score: after 3 months, significantly more patients of the SFT group (39%), compared with the control group (18%), scored below the cut-off score of 35 on the CIS-fatigue ($p = 0.03$). At 6 months, this was 34% and 21%, respectively ($p = 0.19$). At 9 months, 30% of the SFT group and 26% of the CAU group showed lower scores than 35 on the CIS-fatigue scale ($p = 0.66$). Anxiety and depression (HADS scale): at baseline (SFT: 6.1; CAU: 6.1), at 3 months (SFT: 5.0; CAU: 5.9; $p = 0.03$), and at 9 months (SFT: 5.5, CAU: 5.3, $p = 0.70$).
Bias	The working group is minimal and the dropout rate in general is high; moreover, there is no balance between the two sexes, and the study proposes an idea of intervention that seems effective. However, more research or a larger intervention group is needed to come to scientific conclusions that confirm the results of this study.	Disease activity was not reassessed during follow-up. The control group had received some information about the intervention, and this may have affected the results; it would have been interesting to evaluate the effects of the intervention with a follow-up at 18 months.

Table 1. Characteristics of the included studies [43,44].

The approach of these treatments is similar and puts the patient and his or her resources at the forefront. SFT is focused on the solution of the problem and on the strategies that lead to improvement; it guides the person towards the construction of possible methods to achieve the set goals [43–45]. PST focuses on the problem and strategies to deal with it; it aims to increase the ability to cope with the daily difficulties caused by chronic diseases [46].

The second study analyzes the efficacy of SFT in IBD patients, as it proved to be the most effective treatment in the previous study and was tested on a larger number of patients [40]. A total of 40 UC patients and 87 CD patients received treatment. At each follow-up, patients were subjected to the measurement of several variables by means of the completion of various questionnaires: the Disease Questionnaire (IBDQ), EuroQol (EQ-5D), Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), and Fatigue Severity Scale-9 (FSS-9). Fatigue scores recorded prior to the start of the study did not differ by age and gender in either study.

3.3. Outcomes of the Studies

The primary outcome measured by both studies is the influence of SFT on fatigue and quality of life, with secondary outcomes covering the effects of therapies on anxiety, depression, rest, disease activity, and medication use.

3.3.1. Primary Outcomes

In the first study [39], at the three-month follow-up, the CIS total score assessment questionnaire showed a decrease in fatigue in 87% of patients in the SFT group, while in the control group and in the PST the decrease in fatigue affected 45–60% of patients. Moreover, as far as quality of life according to the IBDQ total score is concerned, patients who underwent surgery showed a slightly greater increase than the control group: SFT: 71.4%, PST: 60%, TAU: 50% of patients.

In the second study [40] at the three-month follow-up, the CIS-Fatigue questionnaire showed that 39% of patients in the intervention group compared to 18% in the control group had fallen below the 35-point cut-off level. At six months, patients below the cut-off score were 34% for the intervention group, and 21% for the control group; at nine months, the difference is not significant. The scores are similar for the CIS-total questionnaire.

3.3.2. Secondary-Outcomes

For the first study [39], there were no differences in anxiety and depression before and after the interventions, according to the HADS questionnaire, and there were no differences in medication use and the need for visits.

In the second study [40], anxiety and depression levels with HADS, medication use, sleep quality, disease activity level, and laboratory test parameters are measured, and there are no differences between the two groups.

4. Discussion

This review presents a comprehensive analysis of nursing interventions aimed at alleviating fatigue in patients with IBD, focusing primarily on CD and UC. This review is significant as it addresses a symptom that profoundly affects the well-being of individuals with IBD yet remains challenging to understand and manage in clinical settings.

Despite the novelty of considering fatigue while assessing IBD-related issues (the first papers have been published in the last years of the last century) and of addressing interventions to its management (infliximab has been the first drug that considered fatigue as a separate outcome measure in a randomized controlled trial at the beginning of this century), few resources have been devoted to exploring interventions primarily targeting fatigue in IBD patients [47].

The reassessment of IBD patients with fatigue is mainly oriented to investigate an active disease, exclude anemia or iron or micronutrient deficiency, other medical or psy-

chological comorbidities, and poor sleep quality, and mainly focus on pharmacological interventions. While considering non-pharmacological interventions, if we exclude those addressing the above listed considerations, we can find more or less only suggestions for lifestyle modification [36,47–49].

A Cochrane review was published in 2020 [50], and, while presenting the results of studies assessing Electroacupuncture, Psychotherapy, physical activity advice, and pharmacological interventions, it does not provide nurses with any indication as to what intervention may be part of nursing while caring for IBD patients with fatigue, as well the systematic reviews published on non-pharmacological interventions and on psychological treatments [51,52].

The review highlights the scarcity of research specifically targeting interventions aimed at the management of fatigue in IBD patients, with only two randomized controlled trials identified. The limited number of studies is attributed to the following reasons: very few studies evaluated the effectiveness of care interventions provided by nurses, and among these studies, the primary focus was on improving quality of life rather than managing fatigue.

Although most patients experience persistent fatigue, and psychological factors are known to be associated with it, management strategies focusing on fatigue are lacking, and intervention studies are scarce.

The conclusions from several studies show inconsistent results for these interventions. The Cochrane review by Timmer et al. [53] aimed to assess the effects of psychological interventions (psychotherapy, patient education, relaxation techniques) on health-related quality of life, coping, emotional state, and disease activity in IBD. However, they found no evidence of efficacy in adult IBD patients in general. In adolescents, such interventions may be beneficial, but the evidence is limited. Similarly, von Wietersheim et al.'s review [54] concluded that the results of studies are inconsistent, with only one study showing an indirect influence on the somatic course of the illness, but this study had very small samples and was not randomized.

In this review, the two selected studies evaluated the effectiveness of SFT and PST administered by nurses in reducing fatigue among CD patients.

The studies demonstrated that nurse-administered SFT and PST interventions significantly reduced fatigue and improved the quality of life in CD patients, with these benefits lasting up to 6 months. Similar results have been observed in other conditions, such as cancer-related fatigue, where cognitive therapy has been shown to improve fatigue [55]. However, the small number of participants and high dropout rates suggest that results should be interpreted with caution.

These interventions are applicable to any gender and age, but their effectiveness may vary depending on the context, such as the setting of the intervention. Adherence to treatment was influenced by real-life factors like work and study commitments, which may affect the generalizability of the results.

The limited number of studies and participants prevents generalization to the broader IBD population. Further research is needed to confirm the long-term effectiveness of these interventions, explore their impact on anxiety and depression, and potentially integrate SFT into clinical practice as a cost-effective treatment for fatigue in IBD patients.

With further evidence supporting the efficacy of SFT, this intervention could be implemented in clinical practice to offer IBD patients suffering from fatigue a cost-effective treatment option without side effects, providing an opportunity to meet with peers.

It should be mentioned that further research should also address the possibility of testing the effectiveness for IBD patients of interventions already able to improve fatigue in other chronic conditions. Improving sleep quality through better sleep hygiene practices has been effective in reducing fatigue in chronic pain [56]. Cognitive Behavioral Therapy has been effective in managing fatigue in cancer-related fatigue and chronic fatigue syndrome [57,58], helping patients identify and change negative thought patterns and behaviors that contribute to fatigue. Regular, moderate exercise has been proven to reduce

fatigue in multiple sclerosis [59] and rheumatoid arthritis [60] and can help improve physical fitness and enhance overall well-being. Mindfulness-Based Stress Reduction involves meditation, body scanning, and yoga to reduce stress and enhance coping mechanisms, being beneficial in reducing fatigue and improving quality of life in patients with fibromyalgia and cancer [61,62]. Energy Conservation Techniques have been used successfully in managing fatigue in multiple sclerosis [63] and chronic obstructive pulmonary disease [64], and nurses can teach patients how to conserve energy through pacing and planning activities.

Integrating these nursing interventions into a comprehensive care plan for IBD patients could also be considered as a way of alleviating fatigue and improving their overall quality of life.

Author Contributions: Conceptualization, M.M. and E.B.; methodology, M.M.; formal analysis, M.M. and E.B.; investigation, M.M. and E.B.; writing—original draft preparation, M.M. and E.B.; writing—review and editing, M.M., G.L., E.M., C.I., R.I.C., E.V.S. and D.G.; supervision, D.G. and E.V.S.; project administration, M.M.; funding acquisition, M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

- 1. Czuber-Dochan, W.; Norton, C.; Bredin, F.; Forbes, A.; Nathan, I.; Berliner, S.; Darvell, M.; Gay, M.; Terry, H. Assessing fatigue in patients with inflammatory bowel disease. *Gastrointest. Nurs.* **2014**, *12*, 13–21. [CrossRef]
- 2. Banovic, I.; Gilibert, D.; Cosnes, J. Crohn's disease and fatigue: Constancy and co-variations of activity of the disease, depression, anxiety and subjective quality of life. *Psychol. Health Med.* **2010**, *15*, 394–405. [CrossRef]
- Nathan, I.; Norton, C.; Czuber-Dochan, W.; Forbes, A. Exercise in Individuals With Inflammatory Bowel Disease. *Gastrointest.* Nurs. 2013, 36, 437–442. [CrossRef]
- 4. Vogelaar, L.; van't Spijker, A.; van Tilburg, A.; Kuipers, E.; Timman, R.; van der Woude, C. Determinants of fatigue in Crohn's disease patients. *Eur. J. Gastroenterol. Hepatol.* **2013**, 25, 246–251. [CrossRef]
- Spekhorst, L.M.; Visschedijk, M.C.; Alberts, R.; Festen, E.A.; van der Wouden, E.J.; Dijkstra, G.; Weersma, R.K.; Dutch Initiative on Crohn and Colitis. Performance of the Montreal classification for inflammatory bowel diseases. *World J. Gastroenterol.* 2014, 20, 15374–15381. [CrossRef]
- Lovasz, B.D.; Lakatos, L.; Golovics, P.A.; David, G.; Pandur, T.; Erdelyi, Z.; Balogh, M.; Szita, I.; Molnar, C.; Komaromi, E.; et al. Risk of colorectal cancer in Crohn's disease patients with colonic involvement and stenosing disease in a population-based cohort from Hungary. J. Gastrointest. Liver Dis. JGLD 2013, 22, 265.
- Ordás, I.; Eckmann, L.; Talamini, M.; Baumgart, D.C.; Sandborn, W.J. Ulcerative colitis. *Lancet* 2012, 380, 1606–1619. [CrossRef] [PubMed]
- Vavricka, S.R.; Schoepfer, A.; Scharl, M.; Lakatos, P.L.; Navarini, A.; Rogler, G. Extraintestinal Manifestations of Inflammatory Bowel Disease. *Inflamm. Bowel Dis.* 2015, 21, 1982. [CrossRef] [PubMed]
- Basso, P.; Fonseca, M.; Bonfá, G.; Alves, V.; Sales-Campos, H.; Nardini, V.; Cardoso, C. Association among genetic predisposition, gut microbiota, and host immune response in the etiopathogenesis of inflammatory bowel disease. *Braz. J. Med. Biol. Res.* 2014, 47, 727–737. [CrossRef]
- 10. Ananthakrishnan, A.N. Epidemiology and risk factors for IBD. Nature reviews. Gastroenterol. Hepatol. 2015, 12, 205.
- 11. Lewis, J.D.; Albenberg, L.; Lee, D.; Kratz, M.; Gottlieb, K.; Reinisch, W. The Importance and Challenges of Dietary Intervention Trials for Inflammatory Bowel Disease. *Inflamm. Bowel Dis.* **2017**, *23*, 181–191. [CrossRef]
- Burisch, J.; Pedersen, N.; Čuković-Čavka, S.; Brinar, M.; Kaimakliotis, I.; Duricova, D.; Shonová, O.; Vind, I.; Avnstrøm, S.; Thorsgaard, N.; et al. East-West gradient in the incidence of inflammatory bowel disease in Europe: The ECCO-EpiCom inception cohort. *Gut* 2014, *63*, 588–597. [CrossRef]

- 13. Karlinger, K.; Györke, T.; Makö, E.; Mester, Á.; Tarján, Z. The epidemiology and the pathogenesis of inflammatory bowel disease. *Eur. J. Radiol.* **2000**, *35*, 154–167. [CrossRef]
- 14. Burisch, J.; Jess, T.; Martinato, M.; Lakatos, P.L. The burden of inflammatory bowel disease in Europe. *J. Crohn's Colitis* **2013**, *7*, 322–337. [CrossRef]
- Molodecky, N.A.; Soon, I.S.; Rabi, D.M.; Ghali, W.A.; Ferris, M.; Chernoff, G.; Benchimol, E.I.; Panaccione, R.; Ghosh, S.; Barkema, H.W.; et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases with Time, Based on Systematic Review. *Gastroenterology* 2012, 142, 54.e42. [CrossRef]
- 16. Mehta, F. Report: Economic implications of inflammatory bowel disease and its management. *Am. J. Manag. Care* **2016**, 22 (Suppl. S3), S51.
- 17. van der Valk, M.E.; Mangen, M.J.; Leenders, M.; Dijkstra, G.; van Bodegraven, A.A.; Fidder, H.H.; de Jong, D.J.; Pierik, M.; van der Woude, C.J.; Romberg-Camps, M.J.; et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF alpha therapy: Results from the COIN study. *Gut* **2014**, *63*, 72–79. [CrossRef]
- 18. Colombara, F.; Martinato, M.; Girardin, G.; Gregori, D. Higher Levels of Knowledge Reduce Health Care Costs in Patients with Inflammatory Bowel Disease. *Inflamm. Bowel Dis.* 2015, 21, 615–622. [CrossRef]
- 19. Day, A.S.; Ledder, O.; Leach, S.T.; Lemberg, D.A. Crohn's and colitis in children and adolescents. *World J. Gastroenterol.* 2012, 18, 5862–5869. [CrossRef]
- 20. Minderhoud, I.M.; Oldenburg, B.; van Dam, P.S.; van Berge Henegouwen Gerard, P. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. *Am. J. Gastroenterol.* 2003, *98*, 1088–1093. [CrossRef]
- 21. Bager, P.; Befrits, R.; Wikman, O.; Lindgren, S.; Moum, B.; Hjortswang, H.; Hjollund, N.H.; Dahlerup, J.F. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment. Pharmacol. Ther.* **2012**, *35*, 133–141. [CrossRef]
- Beck, A.; Bager, P.; Jensen, P.E.; Dahlerup, J.F. How Fatigue Is Experienced and Handled by Female Outpatients with Inflammatory Bowel Disease. *Gastroenterol. Res. Pract.* 2013, 2013, 153818. [CrossRef]
- 23. Opheim, R.; Fagermoen, M.S.; Bernklev, T.; Jelsness-Jorgensen, L.; Moum, B. Fatigue interference with daily living among patients with inflammatory bowel disease. *Qual. Life Res.* 2014, 23, 707–719. [CrossRef]
- Maes, M. An intriguing and hitherto unexplained co-occurrence: Depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2011, 35, 784–794. [CrossRef]
- 25. Singh, S.; Blanchard, A.; Walker, J.R.; Graff, L.A.; Miller, N.; Bernstein, C.N. Common Symptoms and Stressors Among Individuals With Inflammatory Bowel Diseases. *Clin. Gastroenterol. Hepatol.* **2011**, *9*, 769–775. [CrossRef]
- 26. Leitner, G.C.; Vogelsang, H. Pharmacological- and non-pharmacological therapeutic approaches in inflammatory bowel disease in adults. *World J. Gastrointest. Pharmacol. Ther.* **2016**, *7*, 5–20. [CrossRef]
- 27. Smith, G.D.; Watson, R.; Roger, D.; McRorie, E.; Hurst, N.; Luman, W.; Palmer, K.R. Impact of a nurseled counselling service on quality of life in patients with inflammatory bowel disease. *J. Adv. Nurs.* **2002**, *38*, 152–160. [CrossRef]
- Sarbagili-Shabat, C.; Sigall-Boneh, R.; Levine, A. Nutritional therapy in inflammatory bowel disease. *Curr. Opin. Gastroenterol.* 2015, 31, 303–308. [CrossRef]
- Belling, R.; McLaren, S.; Woods, L. Specialist nursing interventions for inflammatory bowel disease. *Cochrane Database Syst. Rev.* 2009, 4, CD006597. [CrossRef]
- 30. Krupp, L.B.; LaRocca, N.G.; Muir-Nash, J.; Steinberg, A.D. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol.* **1989**, *46*, 1121–1123. [CrossRef] [PubMed]
- Chalder, T.; Berelowitz, G.; Pawlikowska, T.; Watts, L.; Wessely, S.; Wright, D.; Wallace, E.P. Development of a fatigue scale. J. Psychosom. Res. 1993, 37, 147–153. [CrossRef] [PubMed]
- 32. Fisk, J.D.; Ritvo, P.G.; Ross, L.; Haase, D.A.; Marrie, T.J.; Schlech, W.F. Measuring the functional impact of fatigue: Initial validation of the fatigue impact scale. *Clin. Infect. Dis.* **1994**, *18* (Suppl. S1), S79–S83. [CrossRef] [PubMed]
- 33. Fisk, J.D.; Doble, S.E. Construction and validation of a fatigue impact scale for daily administration (D-FIS). *Qual. Life Res.* 2002, 11, 263–272. [CrossRef] [PubMed]
- 34. Piper, B.F.; Dibble, S.L.; Dodd, M.J.; Weiss, M.C.; Slaughter, R.E.; Paul, S.M. The revised Piper Fatigue Scale: Psychometric evaluation in women with breast cancer. *Oncol. Nurs. Forum.* **1998**, *25*, 677–684. [PubMed]
- O'Connor, M.; Bager, P.; Duncan, J.; Gaarenstroom, J.; Younge, L.; Détré, P.; Bredin, F.; Dibley, L.; Dignass, A.; Gallego Barrero, M.; et al. N-ECCO Consensus statements on the European nursing roles in caring for patients with Crohn's disease or ulcerative colitis. J. Crohn's Colitis 2013, 7, 744–764. [CrossRef] [PubMed]
- 36. Czuber-Dochan, W.; Ream, E.; Norton, C. Review article: Description and management of fatigue in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **2013**, *37*, 505–516. [CrossRef]
- Jonefjäll, B. Gastrointestinal Symtoms and Fatigue in Patients with Quiescent Ulcerative Colitis. Ph.D. Thesis, University of Gothenburg, Göteborg, Sweden, 2016.
- Dibley, L.; Bager, P.; Czuber-Dochan, W.; Farrell, D.; Jelsness-Jørgensen, L.-P.; Kemp, K.; Norton, C. Identification of Research Priorities for Inflammatory Bowel Disease Nursing in Europe: A Nurses-European Crohn's and Colitis Organisation Delphi Survey. J. Crohn's Colitis 2016, 11, jjw164. [CrossRef] [PubMed]

- Vogelaar, L.; Van't Spijker, A.; Vogelaar, T.; van Busschbach, J.J.; Visser, M.S.; Kuipers, E.J.; van der Woude, C.J. Solution focused therapy: A promising new tool in the management of fatigue in Crohn's disease patients psychological interventions for the management of fatigue in Crohn's disease. J. Crohn's Colitis 2011, 5, 585. [CrossRef] [PubMed]
- Vogelaar, L.; Spijker, A.V.; Timman, R.; van Tilburg, A.J.P.; Bac, D.; Vogelaar, T.; Kuipers, E.J.; van Busschbach, J.J.V.; van der Woude, C.J. Fatigue management in patients with IBD: A randomised controlled trial. *Gut* 2014, 63, 911–918. [CrossRef]
- 41. García-Vega, E.; Fernandez-Rodriguez, C. A stress management programme for Crohn's disease. *Behav. Res. Ther.* 2004, 42, 367–383. [CrossRef] [PubMed]
- Liu, W.; Geng, H.; Ma, L.; Liu, F.; Wei, X.; Tian, X.; Liu, L. Effect of the solution-focused brief therapy on cancer-related fatigue in breast cancer patients under adjuvant chemotherapy: A randomized trial. *Transl. Cancer Res.* 2020, *9*, 7405–7414. [CrossRef] [PubMed]
- Bakker, J.M.; Bannink, F.P. [Solution focused brief therapy in psychiatric practice] Oploss-ingsgerichtetherapie in de psychiatrischepraktijk. *Tijdschr. Psychiatr.* 2008, 50, 55–59. [PubMed]
- 44. Smith, S. A preliminary analysis of narratives on the impact of training in solution-focused therapy expressed by students having completed a 6-month training course. *J. Psychiatr. Ment. Health Nurs.* **2010**, *17*, 105–110. [CrossRef] [PubMed]
- Smock, S.A.; Trepper, T.S.; Wetchler, J.L.; McCollum, E.E.; Ray, R.; Pierce, K. Solution-focused group therapy for level 1 substance abusers. J. Marital. Fam. Ther. 2008, 34, 107–120. [CrossRef] [PubMed]
- 46. Nezu, A.M.; Nezu, C.M.; Felgoise, S.H.; McClure, K.S.; Houts, P.S. Project Genesis: Assessing the efficacy of problem-solving therapy for distressed adult cancer patients. *J. Consult. Clin. Psychol.* **2003**, *71*, 1036–1048. [CrossRef] [PubMed]
- 47. van Langenberg, D.R.; Gibson, P.R. Systematic review: Fatigue in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **2010**, *32*, 131–143. [CrossRef] [PubMed]
- 48. Kreijne, J.E.; Lie, M.R.; Vogelaar, L.; van der Woude, C.J. Practical Guideline for Fatigue Management in Inflammatory Bowel Disease. *J. Crohn's Colitis* 2016, *10*, 105–111. [CrossRef]
- Artom, M.; Czuber-Dochan, W.; Sturt, J.; Norton, C. Targets for Health Interventions for Inflammatory Bowel Disease-fatigue. J. Crohn's Colitis 2016, 10, 860–869. [CrossRef] [PubMed]
- 50. Farrell, D.; Artom, M.; Czuber-Dochan, W.; Jelsness-Jørgensen, L.P.; Norton, C.; Savage, E. Interventions for fatigue in inflammatory bowel disease. *Cochrane Database Syst. Rev.* 2020, *4*, CD012005. [CrossRef]
- 51. Davis, S.P.; Bolin, L.P.; Crane, P.B.; Wei, H.; Crandell, J. Non-pharmacological interventions to manage fatigue in adults with inflammatory bowel disease: A systematic review and meta-analysis. *Complement. Ther. Clin. Pract.* 2020, 41, 101229. [CrossRef]
- 52. Emerson, C.; Barhoun, P.; Olive, L.; Fuller-Tyszkiewicz, M.; Gibson, P.R.; Skvarc, D.; Mikocka-Walus, A. A systematic review of psychological treatments to manage fatigue in patients with inflammatory bowel disease. *J. Psychosom. Res.* **2021**, 147, 110524. [CrossRef]
- 53. Timmer, A.; Preiss, J.C.; Motschall, E.; Rücker, G.; Jantschek, G.; Moser, G. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst. Rev.* **2011**, *16*, CD006913. [CrossRef] [PubMed]
- von Wietersheim, J.; Kessler, H. Psychotherapy with chronic inflammatory bowel disease patients: A review. *Inflamm. Bowel. Dis.* 2006, 12, 1175–1184. [CrossRef]
- 55. van der Lee, M.L.; Garssen, B. Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: A treatment study. *Psychooncology* **2010**, *21*, 264–272. [CrossRef]
- 56. Whale, K.; Dennis, J.; Wylde, V.; Beswick, A.; Gooberman-Hill, R. The effectiveness of non-pharmacological sleep interventions for people with chronic pain: A systematic review and meta-analysis. *BMC Musculoskelet. Disord.* **2022**, *23*, 440. [CrossRef]
- Zhang, Q.; Li, F.; Zhang, H.; Yu, X.; Cong, Y. Effects of nurse-led home-based exercise & cognitive behavioral therapy on reducing cancer-related fatigue in patients with ovarian cancer during and after chemotherapy: A randomized controlled trial. *Int. J. Nurs. Stud.* 2018, 78, 52–60.
- 58. Maas Genannt Bermpohl, F.; Kucharczyk-Bodenburg, A.C.; Martin, A. Efficacy and Acceptance of Cognitive Behavioral Therapy in Adults with Chronic Fatigue Syndrome: A Meta-analysis. *Int. J. Behav. Med.* **2024**, 1–16. [CrossRef]
- 59. Heine, M.; van de Port, I.; Rietberg, M.B.; van Wegen, E.E.; Kwakkel, G. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst Rev.* **2015**, 2015, CD009956. [CrossRef]
- 60. Metsios, G.S.; Kitas, G.D. Physical activity, exercise and rheumatoid arthritis: Effectiveness, mechanisms and implementation. *Best Pract. Res. Clin. Rheumatol.* **2018**, *32*, 669–682. [CrossRef]
- Cash, E.; Salmon, P.; Weissbecker, I.; Rebholz, W.N.; Bayley-Veloso, R.; Zimmaro, L.A.; Floyd, A.; Dedert, E.; Sephton, S.E. Mindfulness meditation alleviates fibromyalgia symptoms in women: Results of a randomized clinical trial. *Ann. Behav. Med.* 2015, 49, 319–330. [CrossRef]
- Li, J.; Li, C.; Puts, M.; Wu, Y.C.; Lyu, M.M.; Yuan, B.; Zhang, J.P. Effectiveness of mindfulness-based interventions on anxiety, depression, and fatigue in people with lung cancer: A systematic review and meta-analysis. *Int. J. Nurs. Stud.* 2023, 140, 104447. [CrossRef] [PubMed]

- Blikman, L.J.; van Meeteren, J.; Twisk, J.W.; de Laat, F.A.; de Groot, V.; Beckerman, H.; Stam, H.J.; Bussmann, J.B.; TREFAMS-ACE Study Group. Effectiveness of energy conservation management on fatigue and participation in multiple sclerosis: A randomized controlled trial. *Mult. Scler.* 2017, 23, 1527–1541. [CrossRef] [PubMed]
- 64. Dixit, S.; Borghi-Silva, A.; Bairapareddy, K.C. Revisiting pulmonary rehabilitation during COVID-19 pandemic: A narrative review. *Rev. Cardiovasc. Med.* **2021**, *22*, 315–327. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.